REMARKS

Claims 18-42 are pending in the application. Claims 20-32 and 35-42 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claim 18 has been amended to further clarify the intended subject matter of the claimed invention. No new matter is added by this amendment. Entry of this amendment is respectfully requested. Therefore, claims 18, 19, 33 and 34 are currently being examined on the merits.

Information Disclosure Statement:

The Examiner asserts that references 1-2 and 15-18 and the accompanying Information Disclosure Statement and form 1449 were not found in the parent file. Applicants submit, as Exhibit A, a copy of the Information Disclosure Statement and form 1449 from the parent application (08/822,264), that was mailed October 29, 1998, as indicated at the upper left of page 1. Applicants also submit a copy of the return receipt postcard. This postcard, stamped as having been received at the Patent Office November 2, 1998, demonstrates that the IDS, form 1449, and copies of the six references were received at that date. Applicants respectfully request that the Examiner review these references before issuing the next Office Action.

Claim Objections:

Claim 18 is objected to for the use of the abbreviation "TCDD". The Examiner suggested that the proper name be used instead of the abbreviation (Office Action, page 2). TCDD is a abbreviation for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, also known as "dioxin" (see the specification at, for example, page 1). Accordingly, claim 18 has been amended to replace all instances of "TCDD" with "dioxin". The Examiner is respectfully requested to withdraw the objection to the claims.

Rejections under 35 U.S.C. §§ 101/112, first paragraph:

The rejection of claims 18-19 and 33-34 under 35 U.S.C. § 101 and § 112, first paragraph as allegedly lacking utility was maintained. The Examiner asserts that the evidence from

Falkenstein et al. is insufficient to demonstrate the utility of the claimed CYSTAR polypeptide as a steroid membrane receptor, because the use of terms such as "likely" and "putative" in Falkenstein et al. allegedly indicates that further experimentation is needed (Office Action, page 3).

Applicants respectfully point out that under sections 35 U.S.C. § 101 and § 112, first paragraph of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office

bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The claimed CYSTAR polypeptide has 93% identity with the porcine steroid membrane binding protein of Falkenstein et al. The statement quoted by the Examiner, that the "protein is likely to represent the first putative steroid membrane receptor" does not reflect uncertainty in the result, but rather the conventional phrasing of the scientific literature. The Examiner has not met the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt the asserted utility of the claimed invention. In the previous Office Action (mailed August 2, 2000, Paper No. 10) the Examiner asserted that the claimed polypeptide was "a receptor for which the function is not known", solely because "the protein is not the traditional progesterone steroid receptor which translocates to the nucleus which is well known" (Paper No. 10, pages 4-5). Yet the results taught by both Falkenstein et al. and Wehling clearly demonstrate the existence of a class of membrane bound steroid receptors. In addition, the conclusions of Falkenstein et al., including the line quoted by the Examiner, clearly demonstrate that those of skill in the art (Falkenstein and coauthors) reasonably believed the function of the porcine homolog of CYSTAR to be that of a membrane bound progesterone receptor. The Examiner does not dispute that the 93% homology between the porcine progesterone membrane receptor is convincing evidence that the two proteins share the same function, and thus the same utility.

The Examiner further asserts that the teachings of Wehling do not demonstrate a clear nexus between the function of CYSTAR and reproductive/developmental disorders merely because one of the results presented in Wehling, regarding the effects of progesterone on the spermatozoan acrosome reaction, had been questioned (Office Action, page 4). Applicants respectfully point out that many additional teachings of Wehling support a connection between CYSTAR function and reproductive/developmental disorders. For example, membrane binding

sites for progesterone had been identified on both oocyte and sperm membranes (Wehling, pages 380-381). Progesterone nongenomic action was also known to have effects on reproductive behavior, and as an anesthetic (Wehling, page 384). Thus, in contrast to the Examiner's assertions, there is a clear nexus between the function of CYSTAR and reproductive/developmental disorders. Furthermore, as discussed in Wehling (page 386), possession of steroid membrane receptors was well known to be potentially useful in allowing researchers "to devise agonists; to search for antagonists; to study proximal parts of signaling".

The Examiner also asserts that no nexus exists between CYSTAR and either IL-6 related diseases or toxicological testing in response to dioxin, because the homology between CYSTAR and IL-6, and CYSTAR and the dioxin responsive protein rat 25-Dx, is allegedly too low (Office Action, pages 3-5). Applicants respectfully point out that the homology between CYSTAR and 25-Dx is not "much lower" than that between CYSTAR and the porcine progesterone membrane receptor. The amino acid sequence identity between CYSTAR and rat 25-Dx is 79%, and the two proteins have similar hydrophobicity plots (see the specification, page 12, lines 22-27; and Figures 3A and 3B). This homology is sufficiently high as to indicate a substantial likelihood of similar function. Moreover, since dioxin has been shown to decrease estrogen-inducible gene products, there appears to be two way cross-talk between the intracellular signaling pathways involving steroids and aromatic hydrocarbons (see the specification at, for example, page 2, lines 1-3). Thus even if CYSTAR does not itself bind dioxin, it still plays a role in mediating the responses to toxins such as dioxin, and therefore is of use in toxicological testing. Similarly, there is a high level of homology between 25-Dx, the progesterone membrane receptor, and the transmembrane domain of IL-6. In addition, dioxin exposure modulates immune and inflammatory responses (specification, page 2, lines 20-22), and loss of an estrogen source can produce an elevation of IL-6 and development of osteoclastogenic osteoporosis (specification, page 3, lines 6-18), indicating a link between steroid receptors such as CYSTAR and immune disorders.

Based upon the above evidence, it is clear that one of skill in the art would conclude that the claimed CYSTAR polypeptides and compositions thereof would have specific, real-world utilities in the study of progesterone function through membrane-bound receptors, the treatment

of reproductive and developmental disorders associated with progesterone action, and in toxicology testing. Withdrawal of the rejection of claims 18-19 and 33-34 under 35 U.S.C. §§101/112, first paragraph is therefore respectfully requested.

Written description rejections under 35 U.S.C. § 112, first paragraph:

Claims 18 and 33 have been rejected under the first paragraph of 35 U.S.C. § 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 § U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, Figures 1 and 2). Variants of SEQ ID NO:1, in particular the preferred, more preferred, and most preferred polypeptide variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are

described, for example, at page 13, lines 8-11. Chemical and structural features of SEQ ID NO:1 are described, for example, from page 12, line 21 through page 13, line 1. Given SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having 95% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because "the specification only discloses one subgenus of the human polypeptide" and "the species for the human is not known because some of the amino acids are represented by Xaa for any amino acids or unknown amino acids" (Office Action, page 6). Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate

written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, in addition to functional characteristics. For example, the "variant language" of independent claim 18 recites chemical structure to define the claimed genus:

> 18. A purified polypeptide comprising an amino acid sequence selected from the group consisting of: a) an amino acid sequence of SEQ ID NO:1, b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the

sequence of SEQ ID NO:1, wherein said amino acid sequence encodes a polypeptide whose expression is upregulated by dioxin...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides recited by the claims. Moreover, the functional recitations included only add to the structural characterization of the recited polypeptides. The polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to cytokine/steroid receptor proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as cytokine/steroid receptor proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polypeptides with "a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 220 amino acid residues). This variation is far less than that of all potential cytokine/steroid receptor proteins related to SEQ ID NO:1, i.e., those cytokine/steroid receptor proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the polypeptide genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly* case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. However, there was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

> 4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:

5'-$_{-24}$ GCL$_{-23}$ X$_{-22}$ TY$_{-22}$ TGG-$_{21}$ ATG$_{-20}$ W$_{-19}$ GZ$_{-19}$ X$_{-18}$ TY$_{-18}$ X$_{-17}$ TY$_{-17}$ CCL$_{-16}$ X$_{-15}$TY$_{-15}$ X$_{-14}$ TY$_{-14}$ GCL$_{-13}$ X$_{-12}$ TY$_{-12}$ X$_{-11}$ TY$_{-11}$ GCL$_{-10}$ X$_{-9}$ TY$_{-9}$ TGG$_{-8}$ GGL$_{-7}$ CCL$_{-6}$GAK$_{-5}$ CCL$_{-4}$ GCL$_{-3}$ GCL$_{-2}$ GCL$_{-1}$ TTK$_1$ GTL$_2$ AAK$_3$ CAJ$_4$ CAK$_5$ X$_6$ TY$_6$ TGK$_7$ GGL$_8$ QR$_9$ S$_9$ CAK$_{10}$ X$_{11}$ TY$_{11}$ GTL$_{12}$ GAJ$_{13}$ GCL$_{14}$ X$_{15}$ TY$_{15}$ TAK$_{16}$ X$_{17}$ TY$_{17}$ GTL$_{18}$ TGK$_{19}$ GCL$_{20}$ GAJ$_{21}$ W$_{22}$ GZ$_{22}$ GCL$_{23}$ TTK$_{24}$ TTK$_{25}$ TAK$_{26}$ ACL$_{27}$ CCL$_{28}$ AAJ$_{29}$ ACL$_{30}$ W$_{31}$ GZ$_{31}$ W$_{32}$ GZ$_{32}$ GAJ$_{33}$ GCL$_{34}$ GAJ$_{35}$ GAK$_{36}$ X$_{37}$ TY$_{37}$ CAJ$_{38}$ GTL$_{39}$ GGL$_{40}$ CAJ$_{41}$ GTL$_{42}$ GAJ$_{43}$ X$_{44}$ TY$_{44}$ GGL$_{45}$ GGL$_{46}$ GGL$_{47}$ CCL$_{48}$ GGL$_{49}$ GCL$_{50}$ GGL$_{51}$ QR$_{52}$ S$_{52}$ X$_{53}$ TY$_{53}$ CAJ$_{54}$ CCL$_{55}$ X$_{56}$ TY$_{56}$ GCL$_{57}$ X$_{58}$ TY$_{58}$ GAJ$_{59}$ GGL$_{60}$ QR$_{61}$ S$_{61}$ X$_{62}$ TY$_{62}$ CAJ$_{63}$ AAJ$_{64}$ W$_{65}$ GZ$_{65}$ GGL$_{66}$ ATM$_{67}$ GTL$_{68}$ GAJ$_{69}$ CAJ$_{70}$ TGK$_{71}$ TGK$_{72}$ ACL$_{73}$ QR$_{74}$ S$_{74}$ ATM$_{75}$ TGK$_{76}$ QR$_{77}$ S$_{77}$ X$_{78}$ TY$_{78}$ TAK$_{79}$ CAJ$_{80}$ X$_{81}$ TY$_{81}$ GAJ$_{82}$ AAK$_{83}$ TAK$_{84}$ TGK$_{85}$ AAK$_{86}$ TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAGAGAGATGG AATAAAGCCCTTGAACCA GC polyA-3'

> wherein
>
> A is deoxyadenyl,

G is deoxyguanyl,

C is deoxycytosyl,

T is thymidyl,

J is A or G;

K is T or C;

L is A, T, C, or G;

M is A, C or T;

X_n is T or C if Y_n is A or G; and C if Y_n is C or T;

Y_n is A, G, C or T if X_n is C, and A or G if X_n is T;

W_n is C or A if Z_n is G or A, and C if Z_n is C or T;

Z_n is A, G, C or T if W_n is C, and A or G if W_n is A;

QR_n is TC if S_n is A, G, C or T, and AG if S_n is T or C;

S_n is A, G, C or T if QR_n is TC, and T or C if QR_n is AG; and, script numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence which includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon $-GCL_{24}$ through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass polypeptides encoding naturally-occurring polypeptide variants which

have at least 95% sequence identity to the amino acid sequence of SEQ ID NO:1. Clearly, then, the genus variation of the present claims is less than that of claim 4 of the '740 patent.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 20, 1997. Much has happened in the development of recombinant DNA technology in the 17 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 in addition to functional limitations. The courts have stressed that structural features are important factors to consider in a written

description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

New matter rejections under 35 U.S.C. § 112, first paragraph:

The Examiner further asserts that the claim 18(b) limitation of sequences having at least 95% sequence identity to SEQ ID NO:1 is new matter because the subgeneric invention is allegedly not disclosed in the specification. Applicants respectfully direct the Examiner's attention to the specification at page 13, lines 10-11, which state that "[a] most preferred CYSTAR variant is one having at least 95% amino acid sequence identity to SEQ ID NO:1." Thus the limitation of claim 18(b) does not constitute new matter.

Rejections under 35 U.S.C. § 102:

Claims 18 and 33 are rejected under 35 U.S.C § 102(b) as allegedly anticipated by Friedberg et al. Friedberg et al. disclose a CYP2B12 which has a 4 amino acid sequence identical to SEQ ID NO:1. The Examiner contends that this is an immunologically active fragment. Claims 18 and 33 are also rejected under 35 U.S.C § 102(a) and (e) as allegedly anticipated by Falkenstein et al. and Jacobs et al, respectively. Both references disclose sequences having 93% amino acid identity to SEQ ID NO:1, which the Examiner contends would also comprise immunologically active fragments of SEQ ID NO:1.

Applicants respectfully point out that the claims are directed to "an immunologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1." In other words, the claimed immunologically active fragments generate antibodies that bind specifically to SEQ ID NO:1, not to other polypeptides. The reference fragments cannot generate such antibodies, since of necessity any antibodies generated by these fragments would also bind to the reference polypeptides, which have at most 93% amino acid sequence identity to SEQ ID NO:1. It is well established in patent law that a reference is anticipatory only if all elements of the claimed invention are disclosed in the reference. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994).

Thus none of Friedberg et al, Falkenstein et al., or Jacobs et al. disclose fragments meeting the limitations of claim 18 or dependent claim 33, and the withdrawal of the rejection of claims 18 and 33 as anticipated under 35 U.S.C. § 102 is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,
INCYTE GENOMICS, INC.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 18 has been amended as follows:

18. (**Twice Amended.**) A purified polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1,

b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence of SEQ ID NO:1, wherein said amino acid sequence encodes a polypeptide whose expression is upregulated by [TCDD] dioxin,

c) a biologically-active fragment of the amino acid sequence of SEQ ID NO:1, wherein said fragment encodes a polypeptide whose expression is upregulated by [TCDD] dioxin, and

d) an immunologically active fragment of the amino acid sequence of SEQ ID NO:1 wherein said fragment generates an antibody that specifically binds to the polypeptide encoded by SEQ ID NO:1.